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10/798,111	03/10/2004	Dario Norberto R. Carrara	88066-7900	5916

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WINSTON & STRAWN LLP
PATENT DEPARTMENT
1700 K STREET, N.W.
WASHINGTON, DC 20006

EXAMINER	
SCHLIENTZ, NATHAN W	

ART UNIT	PAPER NUMBER
1616	

NOTIFICATION DATE	DELIVERY MODE
06/05/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@winston.com
mwalker@winston.com

Office Action Summary	Application No.	Applicant(s)	
	10/798,111	CARRARA ET AL.	
	Examiner	Art Unit	
	Nathan W. Schlientz	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-11,13,15-31,37,38,40-47 and 56-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-11,13,15-31,37,38,40-47 and 56-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 1, 3-11, 13, 15-31, 37, 38, 40-47 and 56-67 are pending and will presently be examined on the merits for patentability. No claim is allowed at this time.

Response to Arguments

Applicant's Remarks filed 18 March 2009 have been fully considered but they are not persuasive as discussed herein below.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 1, 5-7, 11 and 64 are rejected under 35 U.S.C. 102(b) as being anticipated by Carrara et al. (WO 02/11768 A1).

Carrara et al. disclose a composition comprising 1.25 wt.% testosterone, 5.00 wt.% diethylene glycol monoethyl ether (Transcutol P), 5.95 wt.% propylene glycol, 43.09 wt.% ethyl alcohol, 43.07 wt.% water, 1.20 wt.% carbomer (Carbopol 980 NF, a gelling agent), 0.38 wt.% triethanolamine (a neutralizing agent), and 0.059 wt.% disodium EDTA (a sequestering agent) (Example 2).

As noted by Applicants on page 11 of their response filed 10 November 2008, Example 2 of Carrara et al. does not contain a long chain fatty alcohol or long chain fatty acid.

Response to Arguments

Applicants argue on page 12 that the formulation of Carrara is characterized by the inclusion of long chain fatty alcohols, and thus teach away from their exclusion. However, as pointed out by Applicants, Carrara et al. disclose a side-by-side comparison wherein the composition of Example 2 (pg. 17, ln. 19-24; and Table VII) does not comprise a long chain fatty alcohol. Therefore, Carrara et al. disclose a composition that comprises all the instantly claimed components and does not comprise a long chain fatty alcohol, long chain fatty acid or long chain fatty ester.

Applicants further argue on page 13 that the present formulation uses different amounts of the components than what is disclosed by Carrara et al. However, the examiner respectfully argues that the amounts listed in Example 2 fall within the ranges of the instant claims, as shown below.

Present Invention	Example 2 of Carrara et al.
At least one active (Testosterone)	Testosterone 1.25 wt.%
Permeation enhancer 0.2-15 wt.%	Diethylene glycol monoethyl ether (Transcutol P) 5.00 wt.%
Polyalcohol 1-15 wt.%	Propylene glycol 5.95 wt.%
Alkanol 5-80 wt.%	Ethyl alcohol 43.09 wt.%
Gelling agent	Carbomer (Carbopol 980 NF) 1.20 wt.%
Neutralizing agent	Triethanolamine 0.38 wt.%
Antioxidant/Sequestering agent	Disodium EDTA 0.059 wt.%
Water	Water 43.07 wt.%

The hydroalcoholic mixture of Carrara et al. (water and ethyl alcohol) is present at 86.16 wt.% wherein the alkanol (ethyl alcohol) is present at 50 wt.% of the mixture and water is present at 50 wt.% of the mixture. The polyalcohol (propylene glycol) and the permeation enhancer (diethylene glycol monoethyl ether) are present in a weight ratio of 1.2:1, and the total amount polyalcohol and permeation enhancer is 10.95 wt.%. Therefore, the composition of Example 2 of Carrara et al., as shown above, fully anticipates the instant claims.

Applicants argue that the composition according to the instant invention comprises balanced amounts of the components to provide permeation enhancement while avoiding undesirable odor and irritation from fatty alcohol or fatty acid compounds. However, the composition according to Example 2 of Carrara et al. possesses the required components in amounts that fall within the instantly claimed range, and does not comprise a fatty acid or fatty alcohol. Thus, the composition according to Example 2 of Carrara et al. fully anticipates the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1,148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1. Claims 1, 5, 6, 8-11, 13, 15-28, 37, 38, 40-47, 56-58 and 61-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mak et al. (US 6,319,913) in view of Bechgaard et al. (US 5,397,771).

Applicant's claims

Applicants claim a gel formulation comprising a sex hormone, a gelling agent, an alkanol, a polyalcohol (propylene glycol), and a permeation enhancer (i.e., tetraglycol furol), wherein the formulation is substantially free of long-chain fatty alcohols, long-chain fatty acids, and long-chain fatty esters; as well as a kit containing said composition and a method for treating hormonal disorders by administering said composition.

Determination of the scope and content of the prior art

(MPEP 2141.01)

Mak et al. teach gel formulations comprising an active ingredient, a penetration enhancing system, a glycol and a gelling agent (col. 2, ln. 19-32). Mak et al. teach that the active ingredient includes hormones, such as testosterone, estradiol and a testosterone derivative, at a concentration of about 0.1 to about 10 wt.%, preferably

about 0.1 to 5 wt.%, more preferably about 1 to about 2 wt.% (col. 4, ln. 1-8) and antioxidants; the penetration enhancing system includes oleic acid at about 0.1 to about 5 wt.%, a C_1-C_4 alcohol (i.e., ethanol, propanol and isopropanol) at about 5 to about 55 wt.%, preferably about 10 to about 40 wt.%, more preferably about 25 to about 35 wt.%, and a glycol (i.e., propylene glycol) at about 25 to about 55 wt.%, preferably about 30 to about 40 wt.% (col. 3, ln. 14-16; col. 4, ln. 9-59); and the gelling agent (i.e., carbomer) at about 1 to about 10 wt.%, preferably about 1 to about 5 wt.%, more preferably about 1 to about 3 wt.% (col. 3, ln. 60 - col. 4, ln. 18). See Tables 1-4 and Examples 1-9 for specific formulations. Example 2 teaches that the preferred compositions for gel products include 0.1-50 wt.% ethanol, 0.1-50 wt.% propylene glycol, 0.1-50 wt.% isopropyl alcohol, 0.1-50 wt.% oleic acid, 0.1-50 wt.% gelling agent, 0.01-50 wt.%, 0.1-50 wt.% additional irritation reducers, 0-0.1 wt.% preservatives, and 0% to saturation drug.

Mak et al. teach that the addition of oleic acid resulted in reduced irritation compared to the addition of oleyl alcohol (Example 1), especially in combination with a gelling agent, such as carbomer (col. 4, ln. 20-24). Mak et al. further teach additional irritation reducers added to the formulations (Examples 2-9), and state that while the combination of oleic acid and gelling agent (Carbopol) produced very low irritating formulations, the incorporation of other irritation reducing agents can further decrease irritation (col. 10, ln. 46-49). Mak et al. also teach that the compositions are suitable for the treatment of menopausal symptoms (col. 5, ln. 55-56) and have utility in people and other mammals suffering from systemic testosterone deficient disorders, wherein these

formulations can be used to deliver testosterone locally, and thus can be used in conditions where increase in local testosterone concentration is beneficial (col. 10, ln. 27-34).

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Mak et al. do not teach gel formulations comprising a permeation enhancer and not comprising oleic acid, as instantly claimed. However, Bechgaard et al. teach 0.1 to 30 wt.%, preferably 0.1 to 20 wt.%, more preferably 1 to 15 wt.% of a n-glycofurol in combination with propylene glycol as a permeation enhancer suitable for intranasal administration of adrenal hormones and sex hormones, such as ethinyloestradiol, levonorgestrel, FSH, LH, LTH, estradiol-17-beta, progesterone, norethindrone, testosterone, etc. and derivatives or analogues thereof (col. 5, ln. 37-40; col. 7, ln. 34-42; and col. 8, ln. 5-26 and 67-68). Bechgaard et al. teach that their formulations are suitable for systemic administration through the mucosa of the nose, mouth or vagina (col. 9, ln. 1-5). Furthermore, Bechgaard et al. teach that n-glycofurols are considered to be a pharmaceutically acceptable carrier, especially a pharmaceutically acceptable carrier for nasal administration, wherein n-glycofurols are considered as an enhancer facilitating the uptake of biologically active substance through a mucosal membrane of a mammal, especially through the mucosa of the nose (col. 9, ln. 6-13). Bechgaard et al. further teach that intranasal administration of n-glycofurol may act just as quickly as intravenous injection (col. 26, ln. 48-50). Bechgaard et al. teach that additional pharmaceutical excipients may be included such as surfactants and pH-controlling

agents (i.e., buffers) (col. 10, ln. 50-52 and 67-68). Also, Bechgaard et al. teach dispensing their compositions from a Pfeiffer pump unit delivering 50 when activated (col. 14, ln. 30-32).

Finding of *prima facie* obviousness

Rational and Motivation (MPEP 2142-43)

Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to substitute n-glycofurol in the place of oleic acid in the formulations of Mak et al. because Bechgaard et al. teach that n-glycofurol is a suitable permeation enhancer for mucosal administration of sex hormones, wherein n-glycofurol may act just as quickly as intravenous administration.

Also, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to substitute n-glycofurol as a functional equivalent to oleic acid as taught by Mak et al. The Supreme Court in KSR International Co. v. Teleflex Inc., 550 U.S. ___, 82 USPQ2d 1385, 1395-97 (2007) identified a number of rationales to support a conclusion of obviousness which are consistent with the proper "functional approach" to the determination of obviousness as laid down in Graham. One such rationale includes the simple substitution of one known element for another to obtain predictable results. The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. See MPEP 2143.

In the instant case, the substituted components (oleic acid and n-glycofurol) and their functions were known in the art at the time of the instant invention. For example, Mak et al. teaches oleic acid as a permeation enhancer for administration of sex

hormones via the mucosa. Bechgaard et al. teaches n-glycofurol as a permeation enhancer for administration of sex hormones via the mucosa. One of ordinary skill in the art could have substituted one known permeation enhancer for another, and the results of the substitution would have been predictable, that is enhanced permeation of the sex hormone through the mucosa.

With regard to the dosage amount and serum levels of hormone, the amounts of hormone in the system that are effective to treat various conditions is well-known to one of ordinary skill in the art. Therefore, it would be within the level of ordinary skill to determine the amount of hormone necessary to achieve therapeutic serum levels. The examiner respectfully points out the following from MPEP 2144.05: "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." I*n re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969); Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed.Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed

invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to Arguments

Applicants argue on page 14 that Mak et al. require a much higher amount of glycol, i.e. about 25-55 wt.%, compared to the present invention, i.e. about 1-15 wt.%. However, it is noted that Mak et al. teach that the preferred gel formulation preferably comprises 0.1-50 wt.% propylene glycol (Example 2). Thus, Mak et al. clearly envisaged gel formulations with as little as 0.1 wt.% propylene glycol. Also, Bechgaard et al. teaches the use of n-glycofurol with water and propylene glycol as a permeation enhancer suitable for mucosal administration. Therefore, one of ordinary skill in the art would have been able to combine n-glycofurol and propylene glycol in the necessary amounts to act as a penetration enhancer, according to Bechgaard et al.

Applicants further argue on page 14 that Mak et al. teach away from the present invention because they teach that oleic acid is far superior to other permeation enhancers in its ability to reduce skin irritation. However, the examiner respectfully argues that Mak et al. state that while the combination of oleic acid and gelling agent (Carbopol) produced very low irritating formulations, the incorporation of other irritation reducing agents can further decrease irritation (col. 10, ln. 46-49). Bechgaard et al. teach that the n-glycofurol containing penetration enhancer compositions resulted in no irritation for the majority of patients tested (Tables 3-5). Therefore, one of ordinary skill in the art would be motivated to use the n-glycofurol based penetration enhancer of

Bechgaard et al. to achieve no irritation, especially since Mak et al. teach that the oleic acid and gelling agent compositions yielded very low irritation, but other irritation reducing agents may be necessary to decrease irritation.

2. Claims 1, 3-11, 13, 15-31, 37, 38, 40-47 and 56-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mak et al. (US 6,319,913) in view of Bechgaard et al. (US 5,397,771), further in view of Dudley et al. (US 6,503,894) and Labrie (US 5,955,455).

Applicant's claims

Applicants claim a gel formulation comprising a sex hormone, a gelling agent, an alkanol, a polyalcohol (propylene glycol), and a permeation enhancer (i.e., tetraglycol furol), wherein the formulation is substantially free of long-chain fatty alcohols, long-chain fatty acids, and long-chain fatty esters; as well as a kit containing said composition and a method for treating hormonal disorders by administering said composition.

Determination of the scope and content of the prior art

(MPEP 2141.01)

The teachings of Mak et al. and Bechgaard et al. are discussed above and incorporated herein by reference.

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Mak et al. and Bechgaard et al. do not teach treating hypogonadism, or the administration of methyltestosterone with methandrostenolone. However, Dudley et al. teach a gel formulation for the treatment of hypogonadism comprising an androgen, alcohol, and penetration enhancer (Abstract), wherein the androgens include testosterone, methyltestosterone, and methandrostenolone (col. 11, ln. 65-66; col. 12, ln. 1 and 17-22; and Table 5). Dudley et al. further teach that suitable penetration enhancers include diethylene glycol monoethyl ether (col. 12, ln. 54-55).

Also, Labrie teaches that dehydroepiandrosterone (DHEA) is useful for the treatment of hypogonadism and conditions related to decreased secretion of sex steroid precursors by the adrenals (Abstract).

Finding of *prima facie* obviousness

Rational and Motivation (MPEP 2142-43)

Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to treat hypogonadism with the compositions of Mak et al., using as the androgen testosterone, methyltestosterone, methandrostenolone, DHEA or combinations thereof, and as the penetration enhancer either n-glycofurol or diethylene glycol monoethyl ether, as reasonably taught by Bechgaard et al. and Dudley et al.

With regard to the combination of methyltestosterone and methandrostenolone, such would have been obvious in the absence of evidence to the contrary because it is generally prima facie obvious to use in combination two or more ingredients that have previously been used separately for the same purpose to form a third composition

useful for that same purpose. The idea of combining them flows logically from their having been taught individually in the prior art. *In re Kerkhoven* 626 F.2d 646, 850, 205 USPQ 1069, 1072 (CCPA 1980).

With regard to the dosage amount and serum levels of hormone, the amounts of hormone in the system that are effective to treat various conditions is well-known to one of ordinary skill in the art. Therefore, it would be within the level of ordinary skill to determine the amount of hormone necessary to achieve therapeutic serum levels. The examiner respectfully points out the following from MPEP 2144.05: "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." I*n re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969); Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed.Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to

one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to Arguments

Applicant's arguments with respect to the instant rejection are the same as their arguments above. Therefore, the examiners response above is incorporated herein by reference.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nathan W. Schlientz whose telephone number is 571-

272-9924. The examiner can normally be reached on 8:30 AM to 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

NWS

/John Pak/
Primary Examiner, Art Unit 1616